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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/361,652 | 07/27/99 | ZUKER C | 2307E-088610 |

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| EXAMINER |
|---|
| BRANNOCK, M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | 9 |

**DATE MAILED:** 04/07/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/361,652 | C.S. Zuker et al. |
| **Examiner** | **Group Art Unit** |
| Michael Brannock, Ph.D. | 1646 |

[X] Responsive to communication(s) filed on *Feb 7, 2000*

[ ] This action is **FINAL.**

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claim**

[X] Claim(s) *1-63* is/are pending in the applicat

Of the above, claim(s) *19-33 and 36-60* is/are withdrawn from consideration

[ ] Claim(s) _____ is/are allowed.

[X] Claim(s) *1, 3, 6-18, and 61-63* is/are rejected.

[X] Claim(s) *2, 4, and 5* is/are objected to.

[X] Claims *1-63* are subject to restriction or election requirement.

**Application Papers**

[X] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

[ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.

[ ] The specification is objected to by the Examiner.

[ ] The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

[ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [X] None of the CERTIFIED copies of the priority documents have been

[ ] received.

[ ] received in Application No. (Series Code/Serial Number) _____.

[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

[X] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

[X] Notice of References Cited, PTO-892

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). *5 and 8*

[ ] Interview Summary, PTO-413

[X] Notice of Draftsperson's Patent Drawing Review, PTO-948

[ ] Notice of Informal Patent Application, PTO-152

***--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---***

## DETAILED ACTION

### *Response to Amendment*

1. Applicant's election with traverse of Group I, claims 1-18, 34, 35 and 61-63 in Paper No. 6, 2/7/00 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I-IV stem from a common concept and theory and are thus related, and also that a search of Groups 1-IV would not be burdensome. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

The term "distinct" means that two or more subjects as disclosed are related, for example, as combination and part (subcombination) thereof, product and process of use, process and product made, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable (novel and unobvious) over each other (though they may each be unpatentable because of the prior art). It will be noted that in this definition the term related is used as an alternative for dependent in referring to subjects other than independent subjects (MPEP § 802.01). Where inventions are related as disclosed but are distinct as claimed, restriction may be proper (MPEP

§ 806(B)). In the previous Office Action, paper 4, 12/30/99, the inventions of Groups I-IV were shown to be distinct, Applicant has not provided arguments as to why the assertion of distinctiveness is improper.

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. Thus, the four groups require divergent searches, and to search all four inventions would be burdensome. Therefore, the restriction is maintained and made final.

***Status of Application: Claims and Amendments***

2. Claims 1-63 are pending

3. Claims 19-33 and 36-60 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6, 2/7/00.

***Priority***

4. This application appears to be related to PCT/US99/17099. However, no priority to this PCT application has been claimed in the declaration or referenced in the 1st paragraph of the specification. Clarification is requested.

***Specification***

5. The disclosure is objected to because of the following informalities: The specification makes reference to several U.S. patent applications, see page 7 lines 25-27, Applicant is required to update the status of same as they change.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 7, and 9-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

a) In claims 7, 9, and 10 the term "stringent conditions" is confusing because it is a relative term and encompasses conditions of varying degrees of stringency. Further, the art does not provide an unambiguous definition and there is no unambiguous definition given for the term in the specification. The specification puts forth examples of stringent conditions (see page 23) but does not clearly define stringent conditions such that the metes and bounds of the claim the applicant is seeking protection for can be determined.

b) Claims 11-18 require "the transmembrane domain", "the extracellular domain" and/or "the cytoplasmic domain". The specification defines "the extra cellular domain" to be the N-terminal region up to about position 563 in one embodiment and to position 580 in another embodiment (see page 12, line 31- page 13, line 4), "the transmembrane domain" to comprise about positions 563-812 containing the seven transmembrane regions as well as extracellular and intracellular loops, and the cytoplasmic domain to comprise the C-terminus beginning with about position 812 (see page 13). These definitions are confusing because in certain embodiments the different domains overlap and it is impossible to determine what applicant considers each of the domains to encompass. Additionally, referring to the N-terminus as *the* extracellular domain is confusing because the extracellular loops that connect the transmembrane regions are recognized in the art as being extracellular domains as well. Likewise, *the* cytoplasmic domain defined by Applicant does not include the cytoplasmic loops which are recognized in the art as being cytoplasmic domains. Likewise, the seven transmembrane regions comprising *the* transmembrane domain are each also recognized in the art as each being transmembrane domains. Further, *the* transmembrane domain defined by Applicant also includes extracellular and intracellular domains. Although Applicant is entitled to be her/his own lexicographer, Applicant cannot ignore the standards of usage in the art. Unfortunately, the art is divided on these issues. Joyce Baldwin, *Curr. Opin. Cell Biol.* 6(180-190)94, shows the extracellular domain of a GPCR to include the N-terminal domain and each of the extracellular loops (see Fig. 1 and page 185, 2nd paragraph). Similarly Baldwin shows the intracellular

domain to be composed of the intracellular loops, and the transmembrane domain to be composed of the transmembrane helices (see Fig 1). Strader, CD et at., *FASEB J.* 3(1825-1832)1989, refers to each transmembrane helix as a "domain", and to the N-terminus, the C-terminus, and the intervening loops as separate entities, (see the Abstract and text). In order to remove the ambiguities associated with this terminology, so that the metes and bounds of the claims can be determined, it is suggested that Applicant amend the claims such that they recite exactly which residues are required by each claim.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3, 6, 8, 10, 11, 12, 14-18, 34, 35 and 61-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a) polynucleotides encoding a polypeptide of SEQ ID NOs: 1, 2 and 3, and antigenic fragments thereof,

b) polynucleotides which hybridize under highly stringent conditions to the polynucleotides of SEQ ID NOs: 4, 5 and 6 - highly stringent conditions ending with a wash step of 65°C, 0.2x SSC and 0.1% SDS.

does not reasonably provide enablement for:

a) polynucleotides which do not hybridize under highly stringent conditions to the polynucleotides of SEQ ID NOs: 4, 5 and 6.

b) polynucleotides which encode amino acid sequence variants of polypeptides of SEQ ID NOs: 1, 2 or 3, or antigenic fragments thereof, and which *also* do not hybridize under highly stringent conditions to the polynucleotides of SEQ ID NOs: 4, 5 and 6.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 3, 6, 8, 10, 11, 12, 14-18, 34, 35 and 61-63 require a nucleic acid encoding a polypeptide that has an amino acid sequence identity that is at least about 70% identical to a polypeptide of SEQ ID NO: 1, 2 or 3.

The specification discloses the tissue specific expression of the polypeptides of SEQ ID NO: 1 (see figure 2), therefore polynucleotides which hybridize under highly stringent conditions to the polynucleotides of SEQ ID NOs: 4, 5 and 6 would be useful as tissue specific markers. Furthermore, polynucleotides which encode a polypeptide of SEQ ID NO: 1, 2 or 3 or antigenic fragments thereof would be useful to produce peptides of SEQ ID NO: 1, 2 or 3 to raise antibodies against to be used as tissue specific markers - these polynucleotides would useful even if they do not hybridize under highly stringent conditions to the polynucleotides of SEQ ID NOs: 4, 5 and 6. However, due to the degeneracy of the genetic code, it cannot be expected that all of the potential polynucleotides that encode polypeptides that are less than 100 % identical to SEQ ID NO: 1, 2 or 3 would be also hybridize under highly stringent conditions to

polynucleotides of SEQ ID No 3, 4, or 5. The specification has not provided more than an invitation to perform further research and investigation into the potential uses of nucleic acids which encode polypeptides that are not identical to the polypeptides of SEQ ID NO: 1, 2 or 3 or antigenic fragments thereof. These "muteins" would not be useful for raising antibodies for use as tissue specific markers as indicated above.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Importantly, these or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 14-16). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of

changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

***Allowable Subject Matter***

10. Claims 2, 4 and 5 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusions***

11. Claims 1, 3, 6-18, 34, 35 and 61-63 are rejected.

12. Claims 2, 4, and 5 are objected to.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Fridays from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D., can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

April 5, 2000

ELIZABETH KEMMERER
PRIMARY EXAMINER